Coalition for Innovative Laboratory Testing
48 Maryland Ave, Suite 400. Annapolis, MD 21401

December 4, 2023

Robert M. Califf, M.D.
Commissioner
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993

Re: ***Comment to Laboratory Developed Tests Proposed Rule***
Docket No. FDA-2023-N-2177

Dear Dr. Califf:

The Coalition for Innovative Laboratory Testing (the "Coalition") respectfully offers the following comment on the Notice of Proposed Rulemaking titled "Medical Devices; Laboratory Developed Tests" (the "Proposed Rule"). Due to the short time permitted for response, this comment is necessarily more cursory and abbreviated than it would have been had our request for a 60-day extension of time been granted.

About the Coalition

The Coalition is an alliance of small businesses that own and operate clinical laboratories that are regulated under the Clinical Laboratory Improvement Amendments of 1988 ("CLIA"). Our companies tend to be entrepreneurial in their development of innovative LDTs that meet unmet medical needs, often access the capital markets, and would be significantly impacted should the rule, as proposed, become finalized. Organized in 2021 in response to the VALID Act legislation, our mandate is to advocate against overly burdensome and duplicative regulations by the FDA while fully supporting upgrades and improvements to the current CLIA rules and practices, especially as they relate to new technologies (AI, NGS, etc.) and today's entrepreneurial laboratory practices (e.g., digital marketing).

Over the past two and a half years the Coalition has organized over 50 meetings with members of Congress, 11 of which involved site visits to CLIA labs in the home states or districts of these elected officials. At least 25 different diagnostics companies have participated in our meetings ranging from entrepreneurial start-ups to firms with over 1,000 employees.

FDA's Small Business Impact Analysis

In their Notice of Proposed Rulemaking, the FDA recognized that the proposed rule "may have relatively greater impact on small laboratories" and specifically requested data and comments on alternatives for such laboratories, such as a longer phase out period. (Federal Register, p. 68023).

Furthermore, the Initial Small Entity Analysis required under the Regulatory Flexibility Act (RFA) for this proposed rule, from FDA's Office of Economic and Analysis, acknowledged the significant burden the rule would impose on smaller labs:

> "The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because most facilities that would be affected by this rule are defined as small businesses and **the proposed rule is likely to impose a substantial burden on the affected small entities, we find that the proposed rule would have a significant economic impact on a substantial number of small entities**…
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> The Small Business Administration (SBA) considers Medical Laboratories (NAICS code 621511) to be small if their annual receipts are less than $41.5 million. Of the 1,200 laboratories, 1,081 laboratories (the sum of all laboratories with less than $41.5 million in annual receipts), or 90 percent of the total, would be small according to the 2023 SBA size standard…
>
> **The estimated annualized cost per small entity ranges from $26,255 to $9,332,409 per laboratory**, depending on its size classification. …**the annualized costs per entity are 22.9 percent of receipts for the small laboratories** (with annual receipts of less than $41,500,000) **making it likely that some small entities in this size category would exit the market or reduce operations as the burden is significant.**" (emphasis added) pp. 110-112

It appears that the above estimates do not include the considerable costs of application fees, which the FDA considers a 'transfer', or the costs of conducting prospective clinical trials that the FDA would require of LDTs that it deems to be "high risk." Those trials can cost tens of millions of dollars and take several years to complete. However, even if the 22.9% of receipts estimated compliance cost is accepted, this would put most small labs out of business. Our polling averages from seven small business participants at a recent Coalition meeting[1] suggests that most of these labs operate with gross margins of about 25% and net profit margins of between 10% to 15%. These numbers are more bullish than lab industry surveys.[2] It is clear therefore that **FDA's estimated cost per compliant lab exceeds net profits forcing most labs to "exit the market or reduce operations" as the FDA Economics Office rather cavalierly concluded.**

The following are some of the key consequences to the U.S. healthcare systems if large numbers of small clinical labs are forced out of the market or required to substantially downsize as predicted by the FDA Economic Office if the Proposed Rule is implemented in its current form:

1. **The current duopoly in the Lab Testing Industry would face less Competition Resulting in Higher Prices, Less Local Access, and Fewer Novel Tests**

[1] Nov. 29, 2023, weekly meeting of the Coalition for Innovative Lab Testing
[2] See e.g., Medical Laboratories Industry Profitability, Gross Margin, Net Margin, Cash Flow Margin, ROE (csimarket.com)

There is an impending duopoly in the clinical lab testing market–Labcorp and Quest Diagnostics. As of 2018, LabCorp and Quest accounted for ~45% of testing by volume, including doctor's offices and hospitals.[3] When accounting for only independent laboratories, this statistic skyrockets, likely closer to 80% of testing by volume. The Proposed Rule would exacerbate, rather than remedy this significant imbalance, thereby reducing price competition, innovation, and local community engagement with and proximity to regional laboratories.

To help lessen or shield them from whatever competition it currently faces from smaller firms, Labcorp has been an active supporter of legislation and rulemaking that burdens these labs with excessive regulation. During their 3rd Quarter 2023 investor earnings call, Labcorp's CEO Adam Schechter admitted that the Proposed Rule would provide them with a "competitive advantage"[4].

Small, independent labs typically develop tests that cost less than those offered by the large lab chains with comparable or superior performance. It is axiomatic in commerce that more competition, not less, will ultimately drive down costs while improving quality.

2. Smaller Market Medical Needs would be Unmet.

Typically, large companies bring to market only those products that address very large markets, and the clinical lab industry is no exception to this practice. Smaller labs, on the other hand, often develop and commercialize tests that address orphan diseases and small patient populations. This practice would largely disappear if most small businesses were put out of business by the implemented rule as predicted by the FDA Economic Office.

3. Timely Test Improvements, Innovation and Accuracy would be Diminished.

While the FDA claims that the Proposed Rule is needed to protect patients it would, paradoxically, have the opposite effect. Today, LDT developers frequently update and improve their tests to incorporate the latest biomarkers and algorithms, especially those powered by machine learning and AI. But the FDA regulations would require developers to obtain prior approval from the agency before making even minor improvements to their tests. This creates a perverse incentive for labs to stagnate rather than innovate since the costs and risks of the latter far exceed the former.

4. Patient / Consumer Choice, Access and Information Flow would be Curtailed.

As we have stated, the premarket approval process will likely cost millions of dollars for each test or assay. For many safe LDTs–which have already been validated and revalidated for many years without adverse events–such a large undertaking cannot be financially justified for low-volume tests. As a result, laboratories will withdraw a staggering number of LDTs from the market. Most likely, those LDTs will disproportionately be ones intended to analyze for rare diseases since they typically are ordered at far lower rates. The Coalition has received dozens of examples of

[3] https://foundersib.com/2018/05/30/labs-diagnostics-news-labcorp-quest/
[4] 360Dx, Oct. 26, 2023

laboratories who offer the only test on the market for rare diseases. When those LDTs are pulled from the market, those patients and their providers will suffer the most harm. Their disease will go undiagnosed, treatment will be delayed, and more expensive and invasive procedures will be required as a result. The FDA did not explore this dynamic, thus the FDA significantly underestimated the expected costs of the proposed rule.

Further, in the Proposed Rule, the FDA made clear that they would be especially restrictive over LDTs marketed directly to consumers. But today, consumers often know more about novel tests than their healthcare providers. Limiting access to information about innovative test opportunities, especially those paid out of pocket, deprives Americans of the freedom to choose tests that inform them of early disease onset. Rather than discouraging direct-to-consumer marketing, the FDA

5. Investment Capital Flow into Diagnostics would be Sharply Reduced

Diagnostics has historically been disfavored by most venture capital investors due to the lack of recurring revenue for tests as compared to drugs. Whereas most pharmaceuticals are consumed daily throughout the course of disease or even over the patient's lifetime, most diagnostic tests are administered at most annually with many only one time-- at disease onset.[5] Our Coalition estimates that fewer than one or two percent of entrepreneurial diagnostics companies receive large amounts of venture capital (more than $50 million) with the overwhelming majority building their companies from individual investors (Angels or equity crowdfunding) and government grants. The Proposed Rule would, for the first time, impose a regulatory regime not unlike those for new drugs with long, expensive prospective clinical trials. Asking investors to support companies with the burdens, but not the benefits of drug development is clearly a losing proposition. Reducing access to investment capital will hasten the demise of promising diagnostics start-ups and stifle innovation.

6. Future Pandemic Responses would be Substantially Impeded

In his *New York Times* bestseller *"Uncontrolled Spread: Why COVID-19 Crushed Us and How We Can Defeat the Next Pandemic"* former FDA Commissioner Scott Gottlieb dedicated nearly 200 pages, more than half of his book, chronicling the failure of testing in the U.S. in the first months of the pandemic and the consequences of this failure. According to Gottlieb, the country needed readily available and accurate diagnostic tests by the end of January 2020, mere weeks after the first cases were discovered here, without which

"we would never catch up with the spread… It was especially important to get diagnostic tests in place quickly, so we could implement widespread testing for the virus and detect cases early, before they led to large outbreaks that we wouldn't be able to control. I feared that the only way to avoid a U.S. epidemic would be through a massive testing capacity that we didn't yet have and would be hard to field without concerted action… Testing would be a major gap in our response and the most visible symptom of the capabilities that we lacked in confronting a public health crisis of this magnitude." (pp.22-24)

[5] Monitoring for diabetes is a rare exception to this rule and as a result much investment has flowed into that space.

"The country had missed the window to field a diagnostic test and deploy it widely enough to detect the early spread, isolate the sick, and try to reduce the scope of transmission. We wouldn't have been able to avert a US epidemic, but we might have delayed its start and reduced its severity. Instead, the virus was heavily seeded across the county." (p. 99)

Gottlieb underscored the need to tap small independent labs in servicing communities across the country:

> "It's also critical that we distribute this infrastructure around the nation. Diagnostic labs need to be close to the population centers to maintain their efficiency. Testing large volumes of patient samples is as much a challenge of logistics as it's a question of having enough testing machines and consumables to process the samples….Getting the patient samples shipped around the country to [LabCorp and Quest Diagnostics] created bottlenecks. National reference labs were strained to take in and process the many thousands of additional packages that were arriving every day by FedEx, filled with swabs. To reduce testing delays, it's important to have the testing sites spread around the country, so that they're close to the points of care." (Emphasis added; pp 272-3)

Most of the small businesses that comprise our Coalition quickly pivoted and conducted hundreds of thousands of COVID-19 PCR tests from 2020 to 2022 before at home rapid antigen tests became widely available. Many contracted with their municipal or county health departments or local school systems to collect specimens, process them and report test results in hours, not days, which was essential to slow transmission and save lives. If, as acknowledged by FDA in their IRFA, most small, community-based labs are forced to close their doors due to the steep costs of the Proposed Rule our nation will be unprepared for the next pandemic or deliberate bioterrorism attack.

Alternatives to the Proposed Rule to Obviate the Aforementioned Consequences

The Regulatory Flexibility Act (RFA) mandates that each initial regulatory flexibility analysis (IRFA) contain a description of "any significant alternatives to the proposed rule which accomplish the stated objectives of applicable statutes, and which minimize any significant economic impact of the proposed rule on small entities. Consistent with the stated objectives of applicable statutes, the analysis shall discuss significant alternatives such as —

(1) the establishment of differing compliance or reporting requirements or timetables that take into account the resources available to small entities;
(2) the clarification, consolidation, or simplification of compliance and reporting requirements under the rule for such small entities;
(3) the use of performance rather than design standards; and
(4) an exemption from coverage of the rule, or any part thereof, for such small entities.[6]

In the IRFA the FDA recognizes that the proposed rule "may have relatively greater impact on small laboratories" and specifically requested data and comments on alternatives for such

[6] RFA section 603(c)

laboratories such as a longer phase out period. (Federal Register, p. 68023). In response to this request, the Coalition offers the following alternatives.

A. Enhance CLIA Standards Rather than Requiring FDA Pre-Market Approval

The Coalition urges FDA to suspend the Proposed Rule and instead utilize its *ex officio* membership on the CDC's Clinical Laboratory Improvement Advisory Committee (CLIAC) to facilitate the creation of clear and comprehensive standards for lab practices not currently addressed in the CLIA rules. These include standards for laboratory communications (lab reports, patient portals, advertisements, etc.) and laboratory analytics (algorithms and AI). The decades old CLIA system provides detailed standards for traditional lab functions such as specimen collection, handling and transport, proficiency testing, specimen analysis, reporting, and laboratory personnel. However, it falls short in offering clear guidelines for how labs should claim their test performance, clinical indications, and the validation required to support those claims.

For example, if a company claims that their lab-developed test is "99% accurate in detecting disease X", what kind of validation should be required to support such a claim? Can it be based on studies using only 10 disease specimens or are 100 or 1000 such specimens required? Are retrospective studies adequate or are prospective trials needed? Does "accurate" refer to sensitivity, specificity, AUC, PPV, NPV, or some other metric? The FDA has considerable expertise in such matters gleaned from many years of regulating medical devices (including IVD test kits and analyzers) and should be sharing this experience with CLIA administrators at CMS and other members of CLIAC. A comprehensive catalog of best practices and standards should be published by CLIAC--replete with specific examples, templates and case studies-- and updated biannually. Labs that fall short of these standards should be notified by federal or state authorities and given an opportunity to respond to or cure deficiencies. Those that fail to do so should have their lab license revoked. But requiring labs to now undergo FDA pre-market approval every time they seek to introduce a new LDT or refine an existing one is regulatory overkill in the extreme, is completely unnecessary to protect patients, and will have dire consequences to our healthcare ecosystem as argued above.

B. Extend the Phase-out Period for Laboratories which are Small Businesses as Suggested by the IRFA

If FDA insists on moving forward with the Proposed Rule rather than adopting our suggested, far less burdensome approach of enhancing CLIA standards, it should extend the phase-out period for small entities by at least three, but preferably six years. This follows the suggestion by FDA's Economics Staff in the IRFA which called for extending the phaseout policy from 4 to 10 years.[7] The proposed rule specifically asked for comments on alternative recommended timelines for smaller laboratories (p. 68023). LDTs that FDA deems to be "high-risk" will likely be required to undergo prospective, randomized clinical trials that cost millions or tens of millions of dollars. In the case of tests intended to screen healthy people or for rare diseases, these clinical trials can often take 3 to 5 years to yield enough positive cases to be statistically meaningful.[8] Giving labs at least 7 years

[7] Laboratory Developed Tests Proposed Rule, *Preliminary Regulatory Impact Analysis,* p. 110
[8] https://www.antidote.me/blog/how-long-do-clinical-trial-phases-take

(rather than the 4 years in the current draft rule) to submit their pre-market approval applications will give them time to try to raise the requisite funding (grants or private investors) and to conduct prospective clinical trials.

C. Require NIH to Set Aside Funds for LDT Clinical Trials Mandated by FDA

As discussed above there has historically been little appetite among venture capital firms to invest in diagnostics due to limited revenue potential as compared to drugs. This disinterest will be multiplied if FDA pre-market approvals become a requirement for LDTs. Thus, if the Proposed Rules are implemented without substantial change the Secretary of HHS should mandate that at least 1% of all NIH extramural funds (which has grown substantially over the past 10 years) be earmarked to fund clinical trials of LDTs seeking FDA approval. This would create a $300 million per year pool that both academic medical centers and small businesses could compete for, likely exceeding the total VC investments in all diagnostics companies in the U.S. in many years.

* * *

The proposed LDT rule represents a fundamental shift in U.S. laboratory regulation and foreseeably will have a profound impact on how clinical laboratories, especially small entities, innovate and deliver laboratory services. We therefore recommend that FDA suspend rulemaking and explore less burdensome approaches described herein.

Sincerely,

Morgan Mills

Morgan Mills
Coalition Advocacy Director
mmills@compassadvocacy.com
Tel. 443-717-4347